claimed antibodies, and which is itself a specific embodiment of the claimed invention;

2) One of ordinary skill in the art would readily be able to make monoclonal antibodies according to the invention, given the teaching of the polyclonal antiserum in the present specification; and

3) The present specification clearly enables one skilled in the art on how to produce and use the Fab fragments of the claimed invention.

In greater detail:

I. The specification clearly enables one skilled in the art how to make and use a polyclonal antiserum containing the claimed antibodies.

Applicants agree with the Examiner that the present specification describes making a polyclonal antiserum. However, applicants strongly disagree with the assertion that the present specification does not disclose the claimed antibody.

The claimed invention is directed to anti-idiotypic vascular endothelial growth factor antibodies. The claims do not limit the antibody to a polyclonal or a monoclonal antibody. Furthermore, the claimed invention does not require that the antibody be isolated or purified to homogeneity. The claimed invention is broadly directed to an antibody which is a ligand of the flk-1 receptor yet not a ligand of the flt-1 receptor.

The polyclonal antiserum is exemplified by the Ig2 J fraction described in the present specification and declaration

by Dr. Plouet filed on March 25, 2002. While the Ig2 J fraction described in the present specification may include some anti-idiotypic antibodies that bind to both flk and flt, the fraction also contains the claimed antibody at a concentration high enough to be detected within the Ig2 J fraction itself (see Figures A and B submitted with the declaration of Dr. Plouet filed on March 25, 2002). Thus, the present specification describes the production of antibodies, albeit within a polyclonal antiserum, which satisfy the recitations of the claims.

Applicants would also like to clarify any confusion regarding the unexpected results exhibited by the present invention in that 15 to 20% of immunized animals produce the claimed antibody. Applicants agree that the animals will not elicit 15 to 20% of monoclonal antibodies. Instead, 15-20% of the immunized animals produced the claimed antibody in their polyclonal antiserum.

While a reaction in 15 to 20% of immunized animals is high, it is believed that this is possible because the nature of anti-idiotype reactions predicts that among a battery of animals immunized with an antibody, each of them will elicit anti-idiotypic antibodies against a limited subset of epitopes born by the primary antibody. This concept is known as "idiotypic restriction". For example, if a primary antibody, such as anti-VEGF antibody, bears 40 different epitopes, each animal will react against a limited number of epitopes varying from one to a

maximum of six epitopes. Thus, the method of eliciting anti-idiotypic antibodies results in a natural selection of antibodies by "idiotypic restriction".

In fact, it is noted that the Radio Receptor Assay set forth in the present application detects antibodies (monoclonal, oligoclonal or polyclonal antibodies) in biological fluids. The assay measures the ability of the antibodies to bind a unique receptor, namely flk-1. The present invention is not devoted to the purification of antibodies. In fact, the purification steps set forth in the present specification are disclosed only for purposes of providing an example.

This purification procedure is not necessary to prove that an anti-idiotypic antibody binds specifically to flk-1. The total preparation already contained antibodies binding to flk-1 and not to flt-1. In other words, this purification procedure was not required for *in vivo* experiments (page 7, line 21) because the natural "idiotypic restriction" had already selected the immune response of the animal against fkl-1 but not against flt-1.

II. <u>One of ordinary skill in the art would readily be able to make monoclonal antibodies according to the invention, given the teaching of the polyclonal antiserum in the present specification.</u>

As noted in the declarations by Dr. Plouet and Dr. Pierre Cazenave filed on March 25, 2002, given the discovery of the claimed antibody in the polyclonal sera of 15-20% of

immunized rabbits, one skilled in the art of idiotopic anti-immunology would expect that a comparable percentage of mice would produce the claimed antibody. In light of the screening methods set forth in the present specification, an analysis of the specificity of mice antibodies by the radio receptor assay would involve only routine experimentation to isolate antibodies of the present invention. For example, when one skilled in the art wants to prepare such monoclonal antibodies, he would have only to follow the procedure descried by Kohler and Milstein. One skilled in the art could readily use this radio receptor assay to screen mouse or rat sera or hybridoma secretion for the ability to bind flk-1.

The procedure for selecting a monoclonal antibody simply requires one to dilute hybridoma cells to obtain clones derived from a single cell. Here again, no additional purification steps will be necessary because the biological material used will behave as an anti-idiotypic antibody from an immunized rabbit (which will have been selected by the idiotypic restriction instead of diluting cells).

Once a positive reaction has been obtained, it means that among the anti-idiotypic antibodies produced by the given animal, at least one B lymphocyte subset synthesizes an antibody of the present specification. Thus, it is believed that the use of the radio receptor assay in this case will predict that the B lymphocyte subset of interest is healthy enough to secrete a

detectable level of antibodies, and that the splenocytes of the animal should be treated with Kohler and Milstein's procedure. It will then be just a matter of time and routine experimentation to obtain monoclonal antibodies by a fusion of the splenocytes of the animal with myeloma cells. The hybridoma cells can then be diluted until a single cell is found that secretes the antibody set forth in the present invention.

Thus, the additional steps for obtaining a monoclonal antibody constitute details that are not required to be placed in the present specification. It is not necessary that every last detail and event should be described, by working examples or otherwise. *Ex parte Wolters et al.,* 214 USPQ 735 (BPAI). Moreover, it is believed that the declarations by Pierre Fons and Pierre-Andre Cazenave demonstrate that obtaining such a monoclonal antibody is simply a matter of routine experimentation. Thus, while it is true that the specification does not read as a production specification or batch record, one of ordinary skill in the art would possess the necessary skills and references to obtain monoclonal antibodies within the scope of the present claims, given the discovery of the antibody itself in the described polyclonal antiserum.

The present claims therefore rightly embrace the novel antibody whether in the form of a polyclonal antiserum fraction or in the form of monoclonal antibodies, as the specification set

forth fully all of the inventive activity needed to arrive at either form.

III. The present specification clearly enables one skilled in the art to produce or use Fab fragments of the claimed invention.

As noted in the declaration by Dr. Plouet filed on March 25, 2002, the Fab fragments of the present invention are ligands for the flk-1 receptor and not the flt-1 receptor. Applicants agree that the Fab fragment of the present invention does not have to exert the same functional activities of an antibody such as dimerization, internalization and self-proliferation. In fact, the claims do not recite these functions. However, the claimed Fab fragment is capable of binding to the flk-1 receptor and not to the flt-1 receptor. It is irrelevant that the Fab fragments do not display each and every property exhibited by the complete antibodies.

The Fab fragments do exhibit the novel binding specificity of the claimed antibodies. The Fab fragments bind to KDR and flk-1 but not to flt. Thus, the Fab fragments block the binding of VEGF to KDR and flt-1, inhibiting the proliferation of endothelial cells. Thus, it is respectfully submitted that the Fab fragments of the present invention are supported by an enabling disclosure of the present specification.

Finally, the Examiner's attention is respectfully directed to the annex of supporting articles. The supporting articles are directed to idiotypic restriction and antibody production.

In view of the foregoing remarks, therefore, it is believed that this application has been placed in condition for allowance, with claims 25-30 and 32-35, as presented. Allowance and passage to issue of the present application is respectfully requested.

Respectfully submitted,

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By _____

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September 18, 2002